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ANALYSIS OF SMALL MOLECULES BINDING WITH DENGUE VIRUS ENVELOPE PROTEIN TRIMER

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Dengue virus is a small enveloped (+)ssRNA virus belonging to Flavivirus genus. It is transmitted by mosquitoes and infects over 300 million people in tropical and equatorial regions annually. There are currently no approved drugs or vaccines against dengue fever. Several viral proteins, including polymerase, methyltransferase, protease, as well as envelope protein E, were suggested as targets for anti-DENV compounds. The E protein plays a crucial role in dengue virus entry, mediating membrane fusion by changing conformation in low pH environment of the endosome through rearrangement of E protein dimers into trimers. The protein unit consists of ectodomain, that includes domains I, II, III and four alpha-helices named the stem and the anchor. The stem binding in the canyon between domains I and II is an essential step to complete the entry stage. Design of small molecules inhibiting stem-trimer interaction is an attractive strategy for the design of new antiviral drugs.

Peptides derived from stem sequence may bind to E protein trimer, thus suppressing virus reproduction in cells. Small molecules may bind to E protein trimer competitively with these peptides. In the recent publication the study results of small molecules and stem oligopeptides competitive binding with E trimer were shown. In a tested series of substances 19 compounds (active molecules set) have demonstrated the inhibiting activity towards the interaction between peptides and E trimer, while 40 compounds (inactive molecules set) have shown no activity [1].

We used docking as a tool to find possible binding sites of the experimentally studied compounds on the surface of the E protein trimer. A set of 285 random molecules from ZINC15 was used as decoys. Molecular weight distribution of the decoy set was fixed to correspond the MW distribution of experimentally tested molecules.

A homology model of NGS strain DENV2 E protein trimer was built in Modeller 9.14 based on the X-ray template (pdb id: 1OK8). Docking was carried out in AutoDock 4. All dockings included 1000 genetic algorithm runs, the protein was treated as rigid, ligands were treated as flexible.

Docking results clusterisation was carried out with RMSD threshold of 8.0 Å. Clusters with similar binding pocket coordinates were attributed to the same binding sites. There were detected 46 sites populated with more than 1000 docked poses taking protein symmetry into account. The score distribution for the most populated clusters was normal for all active, inactive and random molecule sets. The dependence of site population on site index in the sequence sorted in descending order of site population was observed. The sample score means were compared to choose the sites with different docking scores distributions for the active, inactive and random compounds. Five such binding sites were found. Docking with the same parameters was carried out for these binding sites. The analysis of compounds binding modes was done.

Our results improve the understanding of interaction between small molecules and DENV E protein surface. Binding sites found in this work may be used in virtual screening involving large libraries of drug-like compounds.

1. Schmidt A. G. et al. *PLoS Pathogens*, 2012, **8(4)**: e1002627

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